(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041807 A1

(51) International Patent Classification[7]: C07D 401/12, 403/12, 405/12, A61K 31/4523, A61P 3/04

(21) International Application Number: PCT/EP2003/012406

(22) International Filing Date: 4 November 2003 (04.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0225938.0 6 November 2002 (06.11.2002) GB

(71) Applicant (*for all designated States except US*): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): **COULTON, Steven** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **PORTER, Roderick, Alan** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **LAWRENCE, Geoffrey, Mark, Prou**; GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

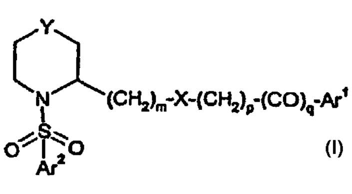
(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/041807 A1

(54) Title: NOVEL COMPOUNDS



(I)

(57) Abstract: This invention relates to N-aryl sulphonyl cyclic amine derivatives of formula (I): and their use as orexin antagonists.

Novel Compounds

This invention relates to *N*-aryl sulphonyl cyclic amine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; and sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-

operative pain; neuralgia; nausea and vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

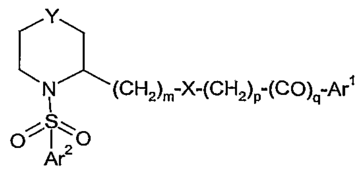
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides *N*-aryl sulphonyl cyclic amine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders. Additionally these compounds are useful in the treatment of stroke, particularly ischemic or haemorrhagic stroke, and/or blocking the emetic response, i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577 and WO00/47580 disclose phenyl urea derivatives and WO00/47576 discloses quinolinyl cinnamide derivatives as orexin receptor antagonists. WO01/96302 discloses N-aroyl cyclic amine derivatives.

According to the invention there is provided a compound of formula (I):



(I)

wherein:

Y represents a bond, oxygen, NQ or a group $(CH_2)_n$, wherein n represents 1, 2 or 3;

m represents 1, 2, or 3;

p represents 0 or 1;

q represents 0 or 1 provided that when q = 1, p = 0;

X is NR, wherein R is H or (C_{1-4})alkyl;

Q is H or (C_{1-4})alkyl;

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 4 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

Preferably m is 1 when p is 0.

In a further preferred embodiment X is NH; m is 1 and p is 0.

Examples of when Ar^1 is a mono or bicyclic heteroaryl are quinoxalinyl, quinazolinyl, pyridopyrazinyl, benzoxazolyl, benzothiophenyl, benzimidazolyl, naphthyridinyl, pyridinyl, pyrimidinyl, thiazolyl, pyridazinyl, pyrazinyl, oxazolyl, triazolyl, imidazolyl, pyrazolyl, quinolinyl, benzofuranyl, indolyl, benzothiazolyl, oxazolyl[4,5-b]pyridiyl, pyridopyrimidinyl, isoquinolinyl, furanyl or thienyl.

Preferably Ar^1 is benzofuranyl, quinoxalinyl, pyridinyl or pyrimidinyl.

When Ar^2 is a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl or pyrazolyl.

When Ar^2 is an optionally substituted bicyclic aromatic or bicyclic heteroaromatic it is selected from benzofuryl, benzimidazolyl, quinolinyl, quinoxalinyl, naphthyl, benzotriazolyl, benzothienyl, benzoxazolyl, naphthyridinyl, isoquinolinyl, quinazolinyl, indolyl, benzothiazolyl, or benzothiadiazolyl.

Preferably Ar^2 represents optionally substituted phenyl, pyridyl, thiazolyl, pyrazolyl, benzofuryl, naphthyl, triazolyl, quinoxalinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothienyl, benzotriazolyl, benzothiazolyl, indolyl or thienyl.

Most preferably Ar^2 represents optionally substituted phenyl or napthyl.

When R^1 is a 5- or 6-membered heterocyclyl group containing up to 4 heteroatoms selected from N, O and S, it may be furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, tetrazoyl, piperazinyl, piperidinyl, morpholinyl or thiomorpholinyl.

Alternatively R^1 is selected from optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl or optionally substituted phenyl.

Preferably R^1 is optionally substituted (C_{1-4})alkoxy, halo, optionally substituted(C_{1-6})alkyl or optionally substituted phenyl.

More preferably R^1 is trifluoromethoxy, trifluoromethyl, methoxy, (C_1)alkyl, chloro, or optionally substituted phenyl.

Optional substituents for the groups Ar^1, Ar^2, R and R^1 include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, hydroxy(C_{1-4})alkyl, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aOCO(CH_2)_r$, $R^aCON(R^a)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring and r represents zero or an integer from 1 to 4. Additional substituents are (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, (C_{1-4})alkylamino(C_{1-4})alkyl, $R^aR^bN(CH_2)n$-, $R^aR^bN(CH_2)nO$-, wherein n represents an integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n$- or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a (C_{3-6})azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

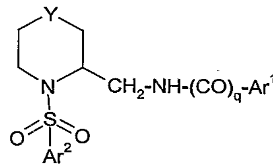
Preferred optional substituents for Ar^2 are halogen, cyano, (C_{1-4})alkyl and (C_{1-4})alkoxy.

Preferred optional substituents for Ar^1 are halogen and cyano.

Preferred optional substituents for R^1 are halogen, (C_{1-4})alkoxy and (C_{1-4})alkyl.

In the groups Ar^1 and Ar^2, substituents positioned *ortho* to one another may be linked to form a ring.

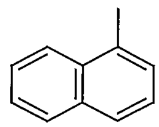
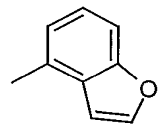
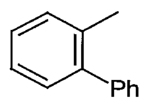
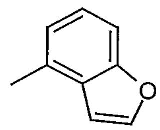
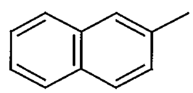
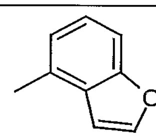
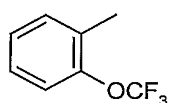
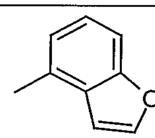
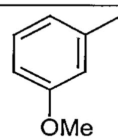
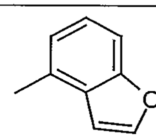
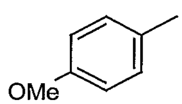
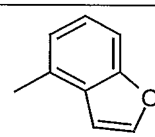
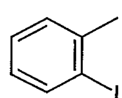
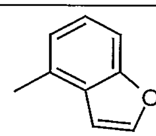
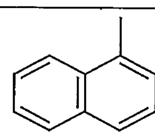
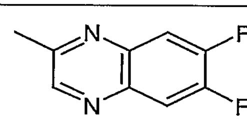
Illustrative compounds of formula (I) are selected from compounds having a core structure (Ia)

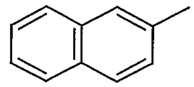
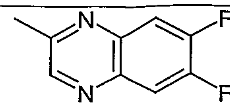
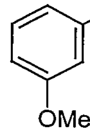
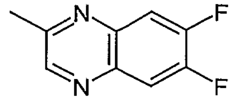
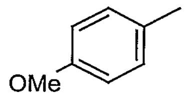
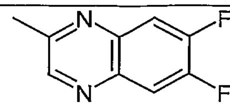
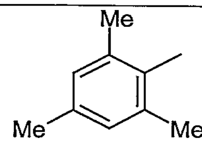
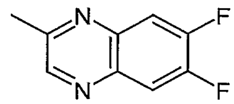
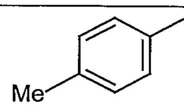
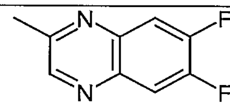
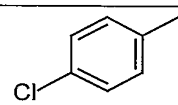
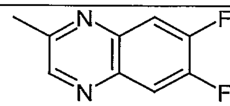
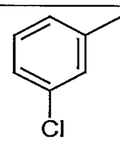
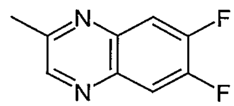
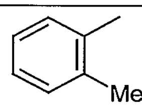
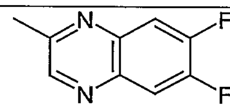
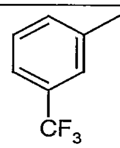
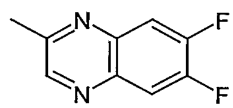
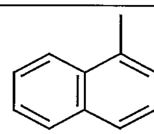
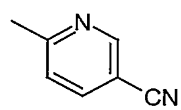
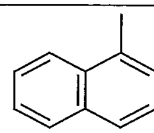
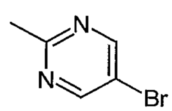
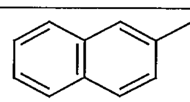
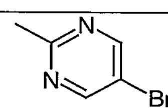
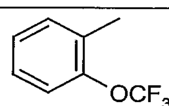
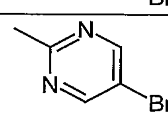


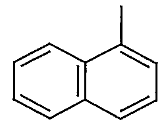
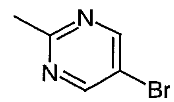
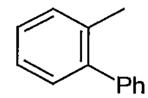
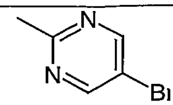
(Ia)

and having Y, q, Ar^1 and Ar^2 as shown in table1:

Table 1

Example	Y	q	Ar^2	Ar^1
1	CH_2	1		
2	CH_2	1		
3	CH_2	1		
4	CH_2	1		
5	CH_2	1		
6	CH_2	1		
7	CH_2	1		
8	CH_2	0		

9	CH_2	0		
10	CH_2	0		
11	CH_2	0		
12	CH_2	0		
13	CH_2	0		
14	CH_2	0		
15	CH_2	0		
16	CH_2	0		
17	CH_2	0		
18	CH_2	0		
19	CH_2	0		
20	CH_2	0		
21	bond	0		

22	bond	0		
23	bond	0		

and pharmaceutically acceptable salts thereof.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

When used herein the term aryl means a 5- to 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further aspect of the present invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following schemes detail some synthetic routes to compounds of the invention.

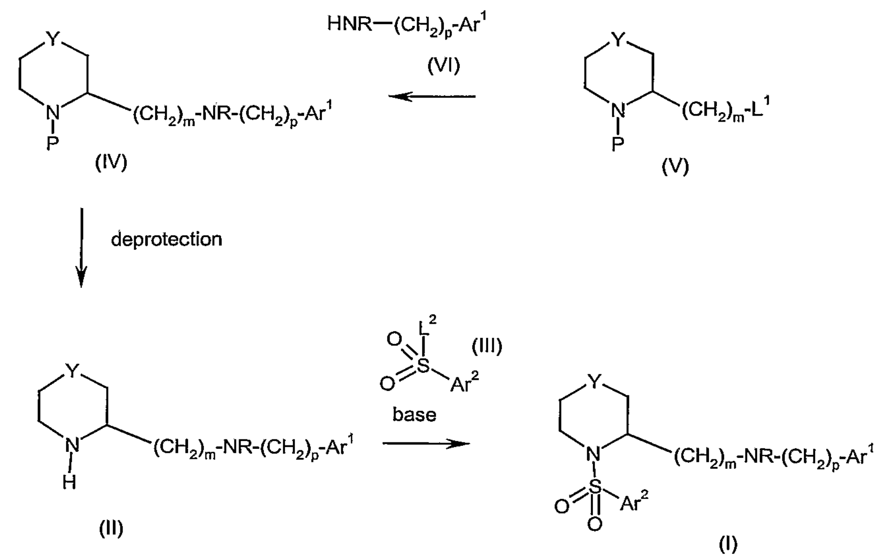
Schemes

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and derivatives thereof. The following are examples of synthetic schemes that may be used to synthesise the compounds of the invention.

Schemes 1a-c may be used for the synthesis of compounds where q = 0.
Scheme 2 may be used for the synthesis of compounds where q = 0 or 1.
Scheme 3-5 may be used for the synthesis of compounds where q = 1.

The compounds labeled (I) in schemes 1 to 5 signify compounds that fall within the generic scope of formula (I).

Scheme 1a



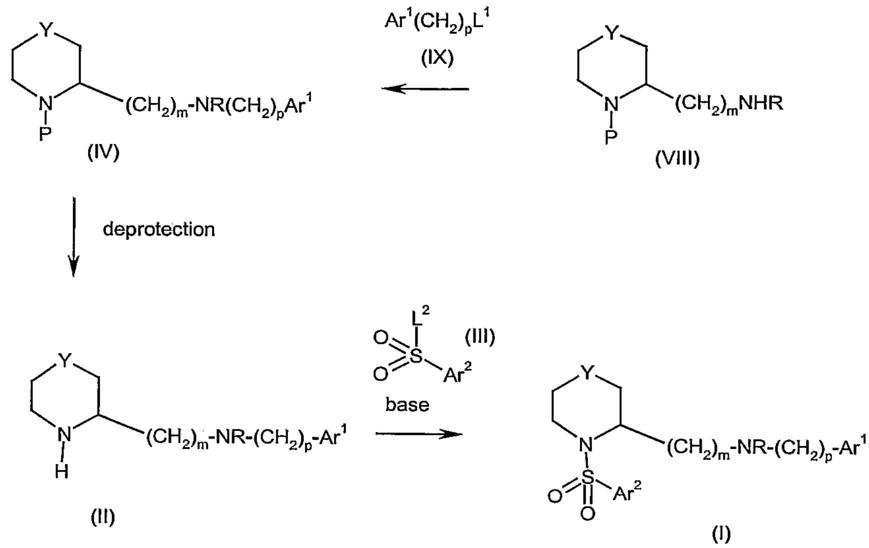
wherein Ar^1, Ar^2, Y, m, p and R are as defined for formula (I), q = 0, L^1 and L^2 are leaving groups, and P is a protecting group.

Examples of suitable leaving groups L^1 include halogen, hydroxy, OSO_2Me, OSO_2(4-tolyl). The reaction of (V) with (VI) preferably proceeds in an inert solvent such as N,N-dimethylformamide in the presence of a base such as triethylamine, sodium hydride or potassium t-butoxide.

An example of a suitable leaving group L^2 is halogen. Sulphonamide formation eg. (II) to (I) may be carried out in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine.

Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl , optionally substitued benzyl and benzyloxycarbonyl. Deprotection conditions are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. sodium hydroxide in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g using palladium on charcoal in a lower alcohol or ethyl acetate).

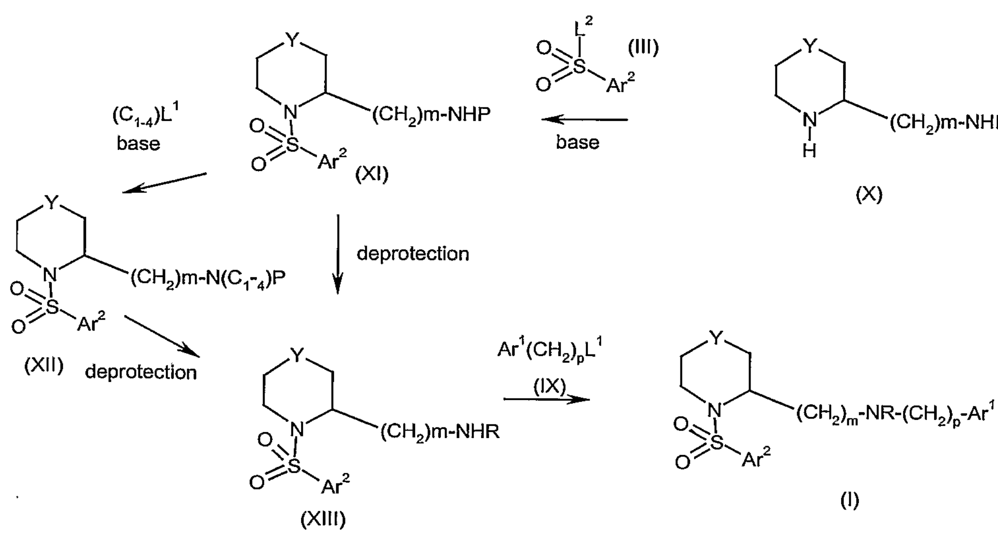
Scheme 1b



Reaction of (VIII) with (IX) proceeds in an inert solvent such as dimethylformamide or xylene in the presence of a base such as potassium carbonate or diisopropylethylamine, preferably at elevated temperatures. P can be a protecting group or H.

Alternatively where m is 1 and p is 0 or 1 compounds maybe prepared as shown in scheme 1c.

Scheme 1c



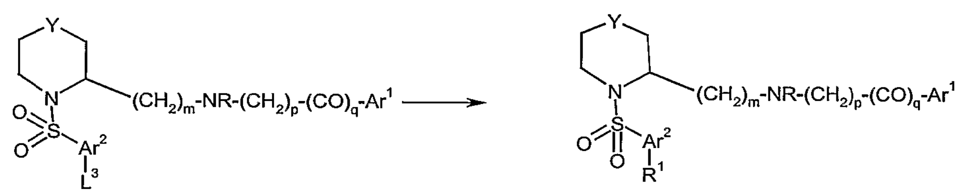
Reaction of (XI) with an alkylating agent $(C_{1\text{-}4})L^1$ proceeds in the presence of a base such as sodium hydride in an inert solvent such as dimethylformamide.

Compounds of formula (V), (VI), (IX), (X) are known in the literature or can be prepared by known methods. Compounds (VIII) can be prepared by known methods.

Within the schemes above there is scope for functional group interconversion; for example in compound (V), conversion of one value of L^1 to another value of L^1; or in compounds (IV) conversion of protecting group P for another protecting group P, or conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents. Where Y = NQ, Q may also represent a protecting group P in the above schemes.

When R^1 is an aromatic group, the substituent R^1 may be introduced at the final stage as illustrated in Scheme 2 by reaction of a compound of formula (VII) where L^3 represents a leaving group such as halogen (preferably bromo or iodo) or trifluoromethylsulfonyloxy, and all other variables are as previously defined, with a reagent R^1M, where M is the residue of an organometallic species e.g. $B(OH)_2$ or trialkylstannyl. Such a process may be carried out in an inert solvent such as 1,2-dimethoxyethane or 1,4-dioxan, in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$.

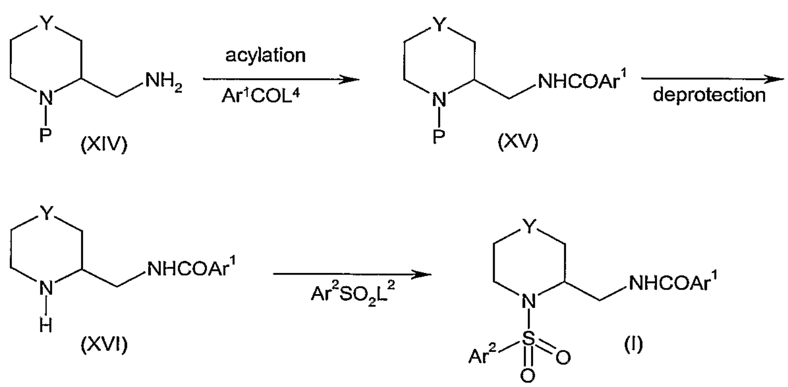
Scheme 2



(VII) (I)

Wherein Ar^2, m, p, q, Ar^1, R, R^1 and Y are as defined for compounds of formula (I). L^3 is a leaving group.

Scheme 3

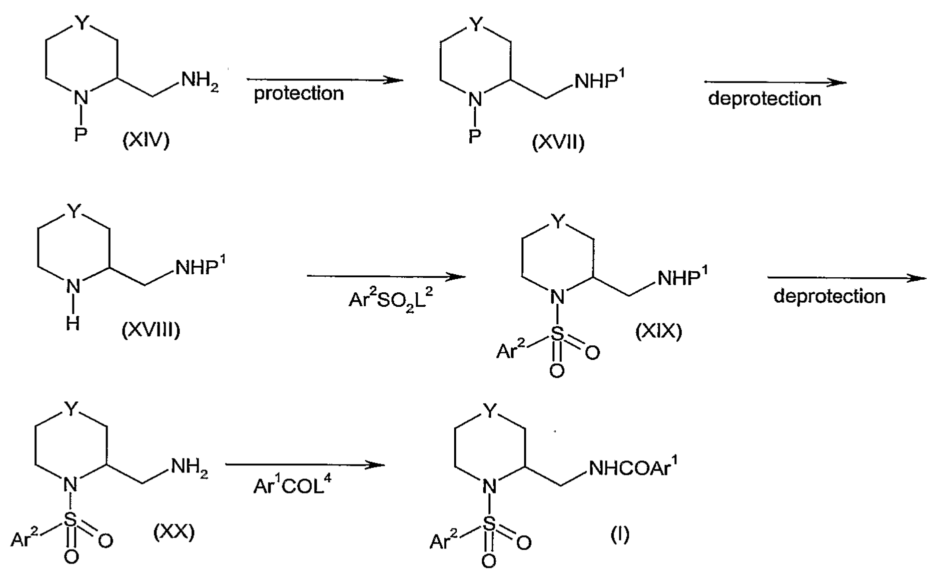


wherein Y, Ar^1 and Ar^2 are as defined for formula (I), P is a protecting group, L^2 is a leaving group as defined above and L^4 is a leaving group.

Examples of suitable leaving groups L^4 include halogen, hydroxy, OC(=O)alkyl OC(=O)O-alkyl and OSO_2Me. Acylation may be carried out using a wide range of known acylation conditions, e.g. in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively these steps may be carried out when L^4 represents hydroxy, in which case the reaction

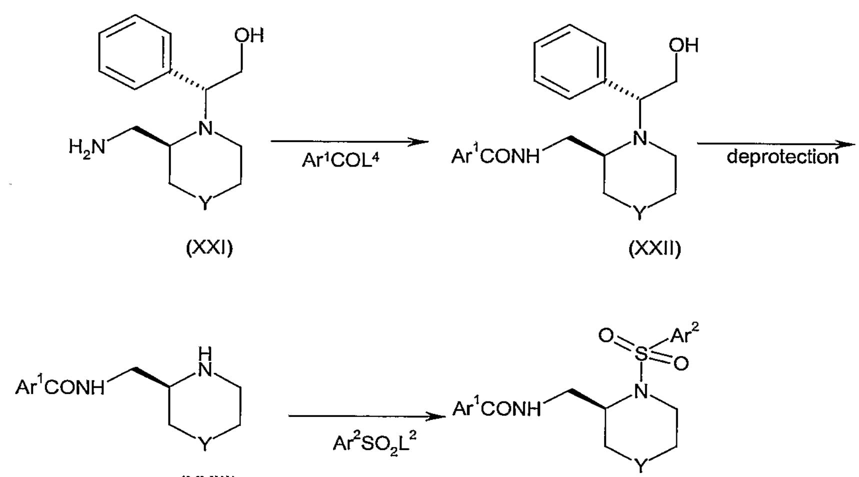
takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

Scheme 4



wherein Y, Ar^1 and Ar^2 are as defined for formula (I), P and P^1 are protecting groups and L^2 and L^4 are leaving groups as defined above. Examples of protecting groups P and P^1 are given in scheme 1a.

Scheme 5



wherein Y, Ar^1 and Ar^2 are as defined for formula (I), and L^1 and L^4 are leaving groups as described above.

Compound (XXI) may be prepared as described in O. Froelich et al., *Tet. Asym.* 1993, 4 (11), 2335 and references therein.

The starting materials for use in Schemes 1 to 5 are commercially available, known in the literature or can be prepared by known methods. Within the schemes above there is scope for functional group interconversion. and for conversion of one value of L^1 to L^4 to another value of L^1 to L^4; or conversion of protecting group P or P^1 to another protecting group P or P^1, or conversion of one compound of formula (I) to another of formula (I) by interconversion of substituents. Where Y = NQ, Q may also represent a protecting group P in the above schemes.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human Orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, and sleep disorders. Additionally the compounds of formula (I) and pharmaceutically acceptable derivatives are useful for the treatment of stroke, particularly ischemic or haemorrhagic and/or in blocking an emetic response i.e. nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional

pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human Orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human Orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochlorohydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human Orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
1 5 10 15
Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30
Leu-NH_2

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional

response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D14 illustrate the preparation of intermediates to compounds of the invention.

Description 1: 2,2,2-Trifluoro-N-[(S)-1-((R)-2-hydroxy-1-phenyl-ethyl)-piperidin-2-ylmethyl]-acetamide

(R)-2-[(S)-2-Aminomethyl-piperidin-1-yl])-2-phenyl-ethanol (20.0g) (Froelich, Olivier; Desos, Patrice; Bonin, Martine; Quirion, Jean-Charles; Husson, Henri-Philippe; Zhu, Jieping., J. Org. Chem. 1996, **61**, 6700) and triethylamine (13.0ml) were dissolved in dichloromethane (500ml), cooled to 0°C and trifluoroacetic anhydride (12.66ml) added dropwise. The mixture was warmed to room temperature and stirred overnight. The organic phase was washed with water, separated, dried and solvent removed at reduced pressure. The residue was column chromatographed [silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant] to give the title compound (28.0g) as a yellow oil. Mass spectrum (API^+): Found 331 (MH^+). $C_{16}H_{21}F_3N_2O_2$ requires 330. $[\alpha]_D$ -55°@ 28° c = 1% in chloroform

Description2: 2,2,2-Trifluoro-N-(S)-1-piperidin-2-ylmethyl-acetamide

The product from D1 (28.0g) was dissolved in ethanol (200ml) containing Pearlmans catalyst (2.0g) and shaken under a hydrogen atmosphere (50psi) at 50°C for 3 hours. The

reaction mixture was filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (14.18g) as a colourless oil. Mass spectrum (API$^+$): Found 211 (MH$^+$). $C_8H_{13}F_3N_2O$ requires 210. $[\alpha]_D$ +18°@ 28° c = 1% in chloroform. ^{1}H NMR δ: (d^6-DMSO) 1.07 (1H, m), 1.32 (2H, m), 1.35 – 1.60 (2H, m), 1.72 (1H, m), 2.54 (1H, t), 2.70 (1H, m), 3.00 (1H, d), 3.17 (3H, m), 9.30 (1H, br. s.)

Description 3: (S)-2-[(2,2,2-Trifluoro-ethanoylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester

The product from D2 (14.18g) was dissolved in dichloromethane (250ml) and treated with di-*tert*-butyl dicarbonate (14.95g). The mixture was stirred for 16h, washed with water, 2N hydrochloric acid and saturated brine, dried and solvent removed at reduced pressure to give the title compound (18.3g). Mass spectrum (API$^+$): Found 311 (MH$^+$). $C_{13}H_{21}F_3N_2O_3$ requires 310. $[\alpha]_D$ -94°@ 28° c = 1% in chloroform. ^{1}H NMR δ: (d^6-DMSO) 1.27 (1H, m), 1.36, 1.47 (9H, s), 1.49 – 1.58 (5H, m), 2.88 (1H, m), 3.22 (1H, m), 3.49 (1H, m), 3.84 (1H, m), 4.34 (1H, m) and 9.42 (1H, br. s.).

Description 4: (S) 2-Aminomethyl-piperidine-1-carboxylic acid *tert* butyl ester

The product from D3 (18.2g) was dissolved in methanol (500ml) and treated with potassium carbonate (16.1g). After stirring for 16h solvent was removed at reduced pressure and the residue partitioned between dichloromethane/water. The organic phase was separated, washed with brine, dried and solvent removed at reduced pressure. the residue was column chromatographed (silica gel, 0 – 10% (9:1 methanol/ammonia) in dichloromethane eluant) to give the title compound (8.82g). Mass spectrum (API$^+$): Found 215 (MH$^+$). $C_{11}H_{22}N_2O_2$ requires 214. $[\alpha]_D$ -32.2°@ 28° c = 1% in chloroform. ^{1}H NMR δ: 1.20 – 1.70 (8H, m), 1.46 (9H, s), 2.64 – 2.80 (2H, m), 2.94 (1H, dd), 3.99 (1H, m) and 4.15 (1H, m).

Description 5: (S)-2-(((1-Benzofuran-4-yl-methanoyl)-amino)-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester

To the amine from D4 (2.14g) in dichloromethane (50ml) was added benzofuran-4-carboxylic acid (1.62g), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.92g) and 1-hydroxybenzotriazole hydrate (0.1g) and the mixture stirred at room temperature for 18h. The reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The organic phase was dried, evaporated and the residue chromatographed on silica gel eluting with a pentane/ethyl acetate gradient to afford the title product as a colurless solid (3g). Mass spectrum (API$^+$): Found 381 (MNa$^+$). $C_{20}H_{26}N_2O_4$ requires 358.

Description 6: Benzofuran-4-carboxylic acid ((S)-1-piperidin-2-ylmethyl)-amide

To the product from D5 (2.9g) in dichloromethane (100ml) was added trifluoroacetic acid (15ml) at room temperature. After 3.5h the mixture was evaporated and the residue partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was

re-extracted with dichloromethane and the combined organic phases dried and evaporated *in vacuo* to afford the title product as a colourless solid (2.17g). Mass spectrum (API$^+$): Found 259 (MH$^+$). $C_{15}H_{18}N_2O_2$ requires 258.

Description 7: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine-1-carboxylic acid *tert* buty ester

The amine D4 (0.607g), and 2-chloro-6,7-difluoroquinoxaline *McQuaid et. al. J. Med. Chem. (1992), 35(18), 3319-24* (0.569g) were dissolved in dimethylformamide (1ml) and heated to 90 °C for 5 days under an atmosphere of argon. After cooling, the reaction solution was partitioned between ethyl acetate and water. The organic layer was washed with water, saturated brine, dried and evaporated. The residue was chromatographed over silica gel, eluting with a gradient of 10 to 50% ethyl acetate in hexane. The title compound was obtained as a pale yellow solid (0.460g), MH$^+$ 379. $C_{19}H_{24}F_2N_4O_2$ requires 378.

Description 8: (S)-2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-piperidine

The product from D7 (0.460g) was dissolved in trifluoroacetic acid (10ml) and stirred at room temperature for 3 hours. The solution was then evaporated and the residue chromatographed over silica gel, eluting with 0 to 10% (9:1 methanol – concentrated ammonia solution) in dichloromethane. The title compound was obtained as a pale yellow foam (0.286g), MH$^+$ 279. $C_{14}H_{16}F_2N_4$ requires 278.

Description 9: (S)-2-[(5-Cyano-pyridin-2-ylamino)-methyl]-piperidine-1-carboxylic acid *tert* butyl ester.

The title compound (1.54g) was prepared from D4 (2.0g) and 2-chloro-5-cyanopyridine (1.29g) in the presence of diisopropylethylamine (1.21g) according to the method of D7. Mass spectrum (API$^+$): Found 317 (MH$^+$). $C_{17}H_{24}N_4O_2$ requires 316.

Description 10: (S)-6-[(Piperidin-2-ylmethyl)-amino]-nicotinonitrile

The title compound (1.56g) was prepared from the compound of D9 (1.53g) and trifluoroacetic acid according to the method of D8. Mass spectrum (API$^+$): Found 217 (MH$^+$). $C_{12}H_{16}N_4$ requires 216.

Description 11: (S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-pyrrolidin-1-carboxylic acid tert butyl ester

(S)-2-Aminomethyl-pyrrolidine-1-carboxylic acid tert butyl ester (5g, 0.025mol) and 5-bromo-2-chloropyrimidine (4.83g, 0.025mol) were combined in xylene (150ml) containing potassium carbonate (10.35g, 0.075mol) and diisopropylethylamine (12.9ml, 0.075mol) and heated under argon at 100^{0}C for 20h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 30% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (4.7g, 53%) as a colourless gum Mass spectrum (API$^+$): Found 257 (MH$^+$ - tert BOC). $C_{14}H_{21}{}^{79}BrN_4O_2$ requires 356.

Description 12: (S)-(5-Bromo-pyrimidin-2-yl)-pyrrolidin-2-ylmethyl-amine
To a solution of D11 (4.7g, 13mmol) in dichloromethane (100ml) was added trifluoroacetic acid (15ml) at room temperature. After 18h the reaction mixture was evaporated and partitioned between dichloromethane and 1M sodium hydroxide. The aqueous phase was extracted with dichloromethane and the combined extracts dried and evaporated to afford the title product (2.72g, 80%). Mass spectrum (API$^+$): Found 257 (MH$^+$). $C_9H_{13}N_4{}^{79}Br$ requires 256.

Description 13: (S)-2-[(5-Bromo-pyrimidin-2-ylamino)-methyl]-piperidine-1-carboxylic acid tert butyl carbonate.
The amine from D4 (1g), 5-bromo-2-chloropyrimidine (0.9g) were combined in xylene (20ml) containing potassium carbonate (1.29g) and diisopropylethylamine (2.43g) and warmed to reflux for 48h. The mixture was cooled to room temperature, filtered and solvent removed at reduced pressure. The residue was column chromatographed (silica gel, pentane – 25% ethyl acetate/pentane). The appropriate fractions were collected, solvent removed at reduced pressure to give the title compound (1.43g) as a colourless gum. Mass spectrum (API$^+$): Found 271 (MH$^+$ - tert BOC). $C_{15}H_{23}{}^{79}BrN_4O_2$ requires 370.

Description 14: (S)-(5-Bromo-pyrimidin-2-yl)-piperidin-2-ylmethyl-amine dihydrochloride
The compound of D13 (2.1 g) was stirred in a mixture of 4M HCl in dioxan/methanol (1:1) for 4 h. Solvent was removed at reduced pressure to give the title compound (1.4g) as a foam. Mass spectrum (API$^+$): Found 271 (MH$^+$). $C_{10}H_{15}{}^{79}BrN_4$ requires 270.

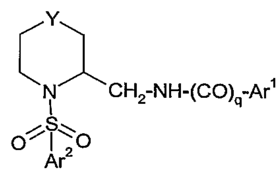
Example 1: Benzofuran-4-carboxylic acid ((S)-1-(naphthalene-1-sulfonyl)-piperidin-2-ylmethyl)amide
1-Naphthalene sulfonyl chloride (0.105g) was added to the amine D6 (0.1g) and triethylamine (0.16ml) in dichloromethane (4ml) at room temperature. After 18h the reaction mixture was washed with saturated sodium bicarbonate solution and the organic layer added directly onto a dry prepacked silica gel cartridge which was eluted with an ethyl acetate/pentane gradient to afford the title product (0.146g). Mass spectrum (Electrospray LC/MS): Found 449 (MH$^+$). $C_{25}H_{24}N_2O_4S$ requires 448.

Example 2: Benzofuran-4-carboxylic acid ((S)-1-(biphenyl-2-sulfonyl)-piperidin-2-ylmethyl)-amide
A mixture of the product from Example 7 (0.465g), phenylboronic acid (0.108g) and sodium carbonate (0.470g) in dimethoxyethane (12ml) and water (12ml) was deoxygenated, tetrakis(triphenylphosphine)palladium (0) ((0.185g) added and the reaction heated under argon at 100^{0}C for 3h. The cooled mixture was filtered, diluted with water and extracted with ethyl acetate. The extracts were dried and evaporated *in vacuo* to a brown gum that was purified on silica gel eluting with an ethyl acetate/pentane gradient to afford the title

product (0.100g). Mass spectrum (Electrospray LC/MS): Found 475 (MH^+). $C_{27}H_{26}N_2O_4S$ requires 474.

In a similar manner Examples 3-23 in the table below were prepared from the amines described in the descriptions above and the appropriate sulphonyl chloride.

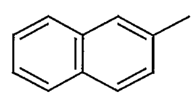
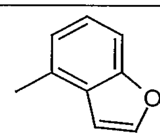
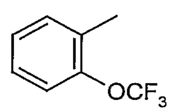
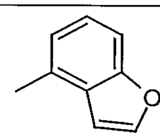
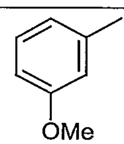
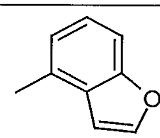
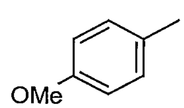
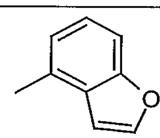
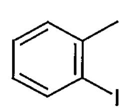
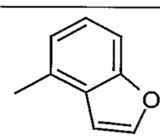
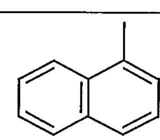
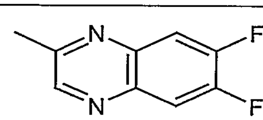
The compounds of examples 3 to 23 have the core structure (Ia)

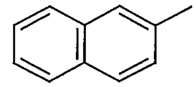
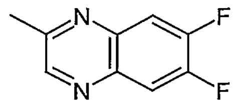
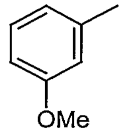
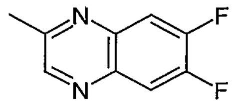
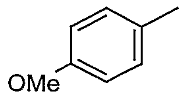
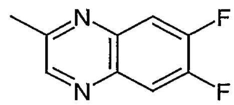
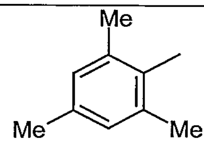
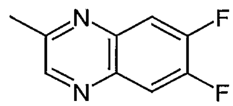
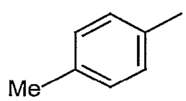
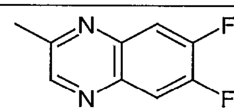
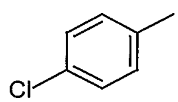
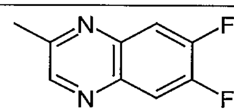
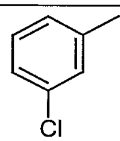
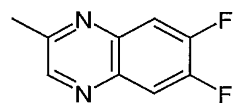
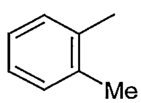
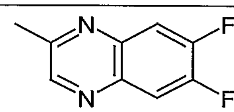
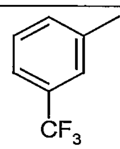
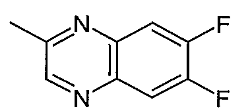
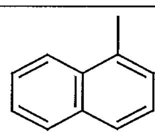
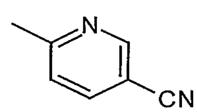
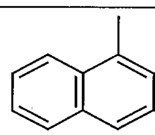
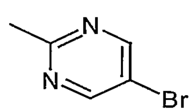
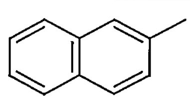
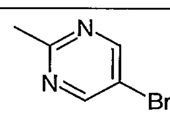
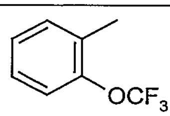
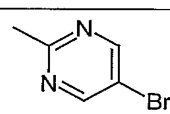


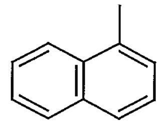
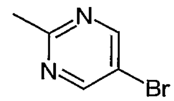
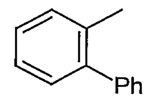
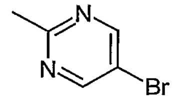
(Ia)

wherein Y, q, Ar^1 and Ar^2 are as indicated in table 2:

Table 2

Example	Y	q	Ar^2	Ar^1	Mass Spectrum (Electrospray LC/MS), API^+
3	CH_2	1			Found: 449 (MH^+) $C_{25}H_{24}N_2O_4S$ requires 448.
4	CH_2	1			Found: 483 (MH^+) $C_{22}H_{21}F_3N_2O_5S$ requires 482.
5	CH_2	1			Found: 429 (MH^+) $C_{22}H_{24}N_2O_5S$ requires 428.
6	CH_2	1			Found: 429 (MH^+) $C_{22}H_{24}N_2O_5S$ requires 428.
7	CH_2	1			Found: 525 (MH^+) $C_{21}H_{21}IN_2O_4S$ requires 524.
8	CH_2	0			Found: 469 (MH^+) $C_{24}H_{22}F_2N_4O_2S$ requires 468.

9	CH_2	0			Found: 469 (MH^+) $C_{24}H_{22}F_2N_4O_2S$ requires 468.
10	CH_2	0			Found: 449 (MH^+) $C_{21}H_{22}F_2N_4O_3S$ requires 448.
11	CH_2	0			Found: 449 (MH^+) $C_{21}H_{22}F_2N_4O_3S$ requires 448.
12	CH_2	0			Found: 461 (MH^+) $C_{23}H_{26}F_2N_4O_2S$ requires 460.
13	CH_2	0			Found: 433 (MH^+) $C_{21}H_{22}F_2N_4O_2S$ requires 432.
14	CH_2	0			Found: 453 (MH^+) $C_{20}H_{19}{}^{35}ClF_2N_4O_2S$ requires 452.
15	CH_2	0			Found: 453 (MH^+) $C_{20}H_{19}{}^{35}ClF_2N_4O_2S$ requires 452.
16	CH_2	0			Found: 433 (MH^+) $C_{21}H_{22}F_2N_4O_2S$ requires 432.
17	CH_2	0			Found: 487 (MH^+) $C_{21}H_{19}F_5N_4O_2S$ requires 486.
18	CH_2	0			Found: 407 (MH^+) $C_{22}H_{22}N_4O_2S$ requires 406.
19	CH_2	0			Found: 461 (MH^+) $C_{20}H_{21}{}^{79}BrN_4O_2S$ requires 460.
20	CH_2	0			Found: 461 (MH^+) $C_{20}H_{21}{}^{79}BrN_4O_2S$ requires 460.
21	bond	0			Found: 481 (MH^+) $C_{16}H_{16}{}^{79}BrF_3N_4O_3S$ requires 480.

22	bond	0			Found: 447 (MH^+) $C_{19}H_{19}{}^{79}BrN_4O_2S$ requires 446.
23	bond	0			Found: 473 (MH^+) $C_{21}H_{21}{}^{79}BrN_4O_2S$ requires 472.

It is understood that the present invention covers all combinations of particular and preferred groups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 minutes. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 seconds (during

continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range 6.9 to 8.6 at the human cloned orexin-1 receptor.

Determination of Orexin-2 Receptor Antagonist Activity

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC50 values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC50 values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5

second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

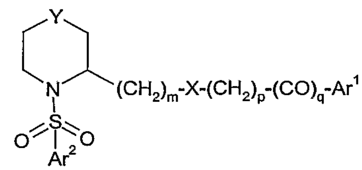
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.4 to 7.6 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

Y represents a bond, oxygen, NQ or a group $(CH_2)_n$, wherein n represents 1, 2 or 3;

m represents 1, 2, or 3;

p represents 0 or 1;

q represents 0 or 1 provided that when q = 1, p = 0.

X is NR, wherein R is H or (C_{1-4})alkyl;

Q is H or (C_{1-4})alkyl

Ar^1 is aryl, or a mono or bicyclic heteroaryl group containing up to 4 heteroatoms selected from N, O and S; any of which may be optionally substituted;

Ar^2 represents phenyl or a 5- or 6-membered heterocyclyl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heterocyclyl group is substituted by R^1 and further optional substituents; or Ar^2 represents an optionally substituted bicyclic aromatic or bicyclic heteroaromatic group containing up to 4 heteroatoms selected from N, O and S;

R^1 represents hydrogen, optionally substituted(C_{1-4})alkoxy, halo, cyano, optionally substituted(C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 4 heteroatoms selected from N, O and S;
or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 where m is 1 when p is 0.

3. A compound according to claim 1 or 2 wherein X is NH.

4. A compound according to claim 1 wherein when Ar^1 is aryl p is not 1.

5. A compound of formula (I) as defined in any one of Examples 1 to 23, or a pharmaceutically acceptable salt of any one thereof.

6. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. Use of a compound of formula (I) as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of disorders where an antagonist of a human Orexin receptor is required.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12406

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D403/12 C07D405/12 A61K31/4523 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/096302 A (BRANCH CLIVE LESLIE ; JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEVIN) 20 December 2001 (2001-12-20) page 2, line 25 - page 3, line 10; claim 1 -----	1-7
A	WO 02/44172 A (BRANCH CLIVE LESLIE ; JOHNSON CHRISTOPHER NORBERT (GB); SMITH ALEXANDE) 6 June 2002 (2002-06-06) page 2, line 26 - page 3, line 13; claim 1 -----	1-7
P,A	WO 03/041711 A (BRANCH CLIVE LESLIE ; JOHNSON CHRISTOPHER NORBERT (GB); NASH DAVID JOH) 22 May 2003 (2003-05-22) page 2, line 26 - page 1, line 14; claim 1 -----	1-7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2004	25/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Usuelli, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02/090355 A (BRANCH CLIVE LESLIE ; JOHNSON CHRISTOPHER NORBERT (GB); THEWLIS KEVIN) 14 November 2002 (2002-11-14) page 2, line 29 - page 3, line 20; claim 1	1-7
X	WO 01/022966 A (SMITHKLINE BEECHAM CORP ; ELLIOTT JOHN D (US); GLEASON JOHN G (US); LE) 5 April 2001 (2001-04-05) claim 1; examples 54,57-59	1-6
X	WO 97/48681 A (FORBES IAN THOMSON ; KING FRANCIS DAVID (GB); RAHMAN SHIRLEY KATHERINE) 24 December 1997 (1997-12-24) page 12; claim 1; example 8	1-6
X	WO 02/02554 A (HOFFMANN LA ROCHE) 10 January 2002 (2002-01-10) claim 1; example 87	1-6
X	DOKUZOVIC, Z.; ET AL: "Asymmetric Synthesis. Metal Complex Mediated Synthesis of Chiral Glycine by Enantioselective Proton Exchange" J.AM.CHEM.SOC., vol. 108, no. 8, 1986, pages 2034-2039, XP002268378 page 2038, right-hand column, line 12 - page 2038, right-hand column, line 42	1-6
X	EP 0 999 205 A (MITSUBISHI TOKYO PHARMACEUTICA) 10 May 2000 (2000-05-10) claim 1; example 73	1-6
X	DATABASE CAPLUS XP002268379 retrieved from STN accession no. 2003:282325 Database accession no. 138:321285 abstract see RNs: 510748-28-4 and 510750-20-6 & WO 03/028641 A (OMODERA KATSUNORI ; SEKIGUCHI YOSHINORI (JP); KANUMA KOSUKE (JP); TAIS) 10 April 2003 (2003-04-10)	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/12406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0196302 A	20-12-2001	AU 7247601 A	24-12-2001
		WO 0196302 A1	20-12-2001
		EP 1289955 A1	12-03-2003
		US 2003186964 A1	02-10-2003
WO 0244172 A	06-06-2002	AU 2488502 A	11-06-2002
		WO 0244172 A1	06-06-2002
		EP 1353918 A1	22-10-2003
WO 03041711 A	22-05-2003	WO 03041711 A1	22-05-2003
WO 02090355 A	14-11-2002	WO 02090355 A1	14-11-2002
WO 0122966 A	05-04-2001	AU 7625500 A	30-04-2001
		EP 1242081 A1	25-09-2002
		JP 2003510278 T	18-03-2003
		WO 0122966 A1	05-04-2001
WO 9748681 A	24-12-1997	AU 3339897 A	07-01-1998
		CA 2258247 A1	24-12-1997
		DE 69720463 D1	08-05-2003
		DE 69720463 T2	15-01-2004
		WO 9748681 A1	24-12-1997
		EP 0912512 A1	06-05-1999
		JP 2000512645 T	26-09-2000
		US 6265408 B1	24-07-2001
WO 0202554 A	10-01-2002	AU 8187701 A	14-01-2002
		BR 0112093 A	13-05-2003
		CA 2413243 A1	10-01-2002
		CN 1440405 T	03-09-2003
		CZ 20030280 A3	17-12-2003
		WO 0202554 A1	10-01-2002
		EP 1299383 A1	09-04-2003
		HU 0301167 A2	28-08-2003
		NO 20026263 A	27-12-2002
		US 2003212066 A1	13-11-2003
		US 2002019424 A1	14-02-2002
EP 0999205 A	10-05-2000	AU 8357198 A	16-02-1999
		EP 0999205 A1	10-05-2000
		CN 1268938 T	04-10-2000
		WO 9905095 A1	04-02-1999
WO 03028641 A	10-04-2003	WO 03028641 A2	10-04-2003